REMARKS

Reconsideration of this application is hereby respectfully requested.

Claims 1-10, 14, and 16-29 are pending in the application. Claims 1, 14, 16, 17-19 and 29 are currently amended. Applicants hereby bring to the Office's attention that related U.S. Patent No. 6,583,108 issued on June 24, 2003 to Tamburini et al. (Tamburini '108) claims the compositions which are at issue in the claimed invention.

Tamburini '108 and the claimed invention contain identical FIGS. 1-14 which are drawn to human bikunin composition and derivations thereof. Tamburini '108 claims a "substantially purified serine protease inhibitor protein containing at least one Kunitz-like domain" (Claim 2). Again, the Tamburini '108 inhibitor is the same inhibitor that is used in the methods of the claimed invention.

Thus, the currently amended claims do not add new subject matter, and do not require a new search, nor do they raise new issues of patentability. In short, the currently amended claims better define and make less vague that which is being claimed.

Applicants believe that the amended claims are in condition to be allowed and such action is respectfully requested.

Turning to the instant Office Action, the following rejections are asserted by the Examiner: Claims 1-10, 13 and 16-18 are rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-10 and 15-18 of co-pending application number 09/441,966; Claims 1-10 are rejected under 35 USC §102(b); and Claims 3-10, 14 and 16-29 are rejected under 35 USC §103(a).

I. Claims 1-10, 13 and 16-18 are rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-10 and 15-18 of co-pending application number 09/441,966.

While Applicants respectfully traverse the rejection, Applicants attach a terminal disclaimer of co-pending Application No. 09/441,966 in compliance with 37 CFR 1.321(c).

II. Claims 1-10 are rejected under 35 USC §102(b). Applicants respectfully traverse the rejection.

A. Rasche et al. teaches the use of a bovine serine protease inhibitor and not a human derived serine protease inhibitor as in the claimed invention.

Claims 1-10 are rejected as being anticipated by Rasche et al. (Rasche). The Office Action states that Rasche anticipates the claimed invention because Rasche teaches use of a Kunitz-type serine protease composition in the treatment of obstructive bronchitis. Applicants hereby respectfully traverse this rejection on the following grounds.

First, Rasche teaches the use of then existing, commercially, available aprotinin derived from bovine (Trasylol; p. 1 of translated article). In contrast, the Kunitz-type protease inhibitor of the claimed invention is derived from human placenta (see for example, p. 17 of specification, "Cloning of Human Bikunin"). One advantage of administering a human composition as in the claimed invention, is that it is less positively charged than the bovine aprotinin inhibitor, or Trasylol (p. 9, line 10; Example 1). A less positively charged human serine protease inhibitor of the claimed invention reduces risk of kidney damage in the patient receiving treatment. A second advantage of the claimed invention is that a protein purified and derived from human tissue has reduced risk of undesired immunological reactions as compared to bovine derived Trasylol (p. 9, lines 12-15), when administered to human patients.

Additionally, certain fragments of the claimed invention (amino acids: 102-159; 7-64; and 1-170) are significantly more potent against plasma kallikrein than Trasylol *in vitro* (Examples 3-4 and 10; p. 9, lines 15-19). Hence, it is expected that the human equivalent will also be more effective *in vivo* relative to the bovine Trasylol.

Therefore, the "method for accelerating the rate of mucociliary clearance in subject with mucociliary dysfunction comprising administering to the subject an effective mucociliary clearance stimulatory amount of a composition comprising a substantially purified serine protease inhibitor protein containing at least one Kunitz-like domain (claim 1)" is not anticipated by Rasche because Rasche teaches the use of a bovine aprotinin protein (Trasylol).

B. Rasche does not teach "each and every element" as set forth in the claimed invention.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ 1051, 1053 (Fed. Cir. 1987). Further, the "identical invention must be shown in as complete detail as is contained in the ...claim." Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Rasche does not teach "each and every element" of the claimed invention. For example, Rasche does not teach the specific sequences as recited in claims 14. 18 and 19 of the claimed invention. As described in the specification, specific sequences of the claimed inhibitor have shown to be more effective. In contrast, Rasche uses a commercially available bovine aprotinin (Trasylol), so there are no teachings of specific sequences as in the claimed invention.

Thus, absent "each and every element" of the claimed invention (i.e. human purified serine protease inhibitor protein containing at least one Kunitz-like domain; and specific domains including but not limited to, SEQ ID NO.: 49; SEQ ID NO.: 2; SEQ ID NO.: 45; SEQ ID NO.: 47; SEQ ID NO.: 71; SEQ ID NO.: 70; SEQ ID NO.: 4; SEQ ID NO.: 5; SEQ ID NO.: 6; SEQ ID NO.:7; SEQ ID NO.: 3; SEQ ID NO.: 50; SEQ ID NO.: 1; SEQ ID NO.: 52; and SEQ ID NO.: 8), there can be no 35 USC 102 rejection.

Therefore, claims 1-10 are not anticipated by Rasche because Rasche alone does not teach "each and every element" of the claimed invention. Claims 1-10 are in good condition to be allowed and such action is respectfully requested.

III. Claims 3-10 and 14 and 16-29 are rejected under 35 USC §103(a). Applicants respectfully traverse the rejection.

A. Claims 3-10 are rejected as being unpatentable over Rasche in view of the state of the art.

In order for a 35 USC §103 rejection to be valid the "claimed invention as a whole must be considered." MPEP 2141; MPEP 2141.02. Further, content of the prior art is determined at the time the invention was made to avoid hindsight.

As mentioned above, the claimed invention uses a human derived serine protease inhibitor and not a bovine inhibitor (Trasylol) as taught by Rasche. At the time Rasche was made (1975) substantially purified human serine protease (subject matter of Tamburini '108 patent) was not available nor was it known. Rasche used Trasylol because it "appeared to be the most suitable for [their] research" in 1975. Thus, the "gist" of the teachings of Rasche does not make the claimed invention, because Rasche was only able to use Trasylol, a bovine serine protease (aprotinin).

Hence, claims 3-10 are patentable and unobvious over Rasche in view of the state of the art, because at the time Rasche was made, the equivalent human aprotinin did not exist.

Therefore, claims 3-10 are in condition to be allowed and such action is respectfully requested.

B. Claims 14 and 16-29 are rejected as unpatentable over Delaria et al. in view of Rasche, Fritz et al., and O'Riordan et al, Applicants respectfully traverse the rejection.

Claims 14 and 16-29 have been amended to incorporate the claim language of the Tamburini '108 patent relating to the human "purified serine protease inhibitor protein containing at least one Kunitz-like domain (claim 1 of Tamburini '108)."

A *prima facie* case of obviousness requires that the Office show some motivation or suggestion in the cited references, or generally available to one of ordinary skill in the art at the time the invention was made; where one skilled in the art working at the time on the problem invention solved would have been motivated or guided by the cited references to combine or modify the cited references to produce the claimed invention. In re Napier, 34 USPQ 2d 1784 (Fed. Cir. 1995).

Discussions of the stated prior art have been discussed in detail previously (response to June 18, 2003 Office Action). However, the claims have been amended to improve their form, thus the following will briefly clarify why the combination of Delaria in view of the other prior art does not make the claimed invention obvious and unpatentable.

First, Delaria teaches the characterization of bikunin 1-170 and that it inhibits serine proteases; Delaria does not teach nor do they suggest the use of bikunin as a therapeutic for the treatment of any disease including mucociliary clearance (MCC) as recited in the methods of the claimed invention. Secondly, Rasche (discussed above) teaches bovine aprotinin as a treatment to

improve lung function; Rasche does not suggest use of a human serine protease inhibitor. Fritz teaches variants of human bikunin as treatments for various ailments; Fritz does not teach that these variants are effective against MCC. .Lastly, O'Riordan teaches antigen-induced bronco constriction is associated with impairment of MCC and that an inhibitor of neutrophil elastase (which is commonly known to be involved implicated in chronic obstructive pulmonary disease), may be useful. However, O'Riordan does not teach nor suggest what that inhibitor might be.

Thus, there is no suggestion in any of the prior art, alone or combined, which would provide the motivation necessary to combine the references as the Office Action has stated. This is because, one of ordinary skill in the art would look the teachings of the claimed invention accelerate the rate of mucociliary clearance in subjects with mucociliary dysfunction comprising administering to the subject an effective mucociliary clearance stimulatory amount of a composition comprising a substantially purified serine protease inhibitor protein containing at least one Kunitz-like domain (amended claim 1).

Therefore, claims 14 and 16-29 are in condition to be allowed and such action is respectfully requested.

IV. Conclusion

In conclusion, Applicants maintain that amended claims 1-10, 14 and 16-29 clearly and patentably define the invention and respectfully request the allowance of the claims which are now pending.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicant's representative can be reached at (858) 677-1456.

The Commissioner is hereby authorized to charge any other fees associated with the filing submitted herewith, or credit any overpayment, to Deposit Account No. 50-1355.

Respectfully submitted,

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